Exhibit 41

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Sprue-like histology in patients with abdominal pain taking olmesartan compared with other angiotensin receptor blockers

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ABSTRACT

Aims A severe syndrome characterised by life-threatening diarrhoea and severe sprue-like histology has been described in patients taking the angiotensin receptor blocker (ARB) olmesartan. It is unknown whether there are any histopathological changes in patients without severe diarrhoea exposed to this medication. It is also unknown whether other ARBs cause sprue-like histology.

Methods Retrospective cohort study of patients with abdominal pain undergoing upper gastrointestinal endoscopy with duodenal biopsy who were taking ARBs. Patients taking olmesartan (n=20) and a non-olmesartan ARB (n=20) were compared with age and sex-matched controls. Histological features (classic sprue-like and other inflammatory changes) were analysed.

Results No single histopathological finding was significantly more common in olmesartan-using patients than controls. However, 10 of 20 olmesartan patients had one or more sprue-like histological features compared with 4 of 20 age-matched and sex-matched controls not taking ARBs (p=0.10). Patients taking ARBs other than olmesartan were not more likely than controls to have one or more of these sprue-like histological features (9/20 vs. 12/20, p=0.34).

Conclusions There were no statistically significant differences between olmesartan users with abdominal pain and controls for any single histopathological abnormality. However, there were trends towards significance for individual abnormalities as well as for a composite outcome of sprue-like changes. This raises the possibility that there is a spectrum of histological changes associated with olmesartan use.

INTRODUCTION

Olmesartan medoxomil is a commonly used antihypertensive medication, which acts by blocking angiotensin receptors. Recently, a series of cases were described in which 22 patients presented with debilitating diarrhoea and had a sprue-like enteropathy on histological examination due to olmesartan. The diarrhoea was so severe that 14 patients required hospitalisation and 4 required total parenteral nutrition. Serological testing for coeliac disease was negative in all cases and none improved with a gluten-free diet. All had biopsies, which showed severe sprue-like changes (villous atrophy, lamina propria inflammation and intraepithelial lymphocytosis (IEL)). Seven of the patients had collagenous sprue. All patients had dramatic improvement, with resolution of their diarrhoea following cessation of olmesartan.[1] As a major referral centre for coeliac disease, we have subsequently encountered a number of such cases and several other case series and reports have been published, which demonstrate similar clinical and histopathological findings.[2–12] At present, this adverse drug reaction is thought to be a rare occurrence. A recent case–control study did not show an association between olmesartan use and chronic diarrhoea in patients presenting for oesophagogastroduodenoscopy (OGD) or colonoscopy.[13]

While it is unusual to encounter severe villous atrophy in non-coeliac patients, milder changes which may overlap with sprue-like enteropathies (such mild or focal IEL) are common.[2 14] Medication reactions, particularly non-steroidal anti-inflammatory drugs, are commonly listed in the differential of such pathological findings.[15] Other drugs also enter the differential, but it is unknown whether olmesartan exposure should be considered when encountering such findings. It is also unknown whether other angiotensin receptor blockers (ARBs) may cause histopathological changes.

Because it is unclear whether the severe sprue-like enteropathy seen in a few patients taking olmesartan is the severe end of a spectrum of intestinal injury, we identified patients taking olmesartan who had undergone endoscopy for abdominal pain with duodenal biopsy and systematically studied the biopsies. We also identified patients with abdominal pain taking other ARBs who had duodenal biopsy and examined their biopsies to determine whether the changes were specific for olmesartan. We identified those patients whose indication for the procedure was abdominal pain to avoid those whose symptom was diarrhoea.

METHODS

We performed a retrospective cohort study using the electronic medical record of Columbia University Medical Center endoscopy unit (ProVation Medical Systems, Wolters Kluwer Health, New South Wales, Australia). This record includes all home medication use reported by outpatients undergoing OGD. This list of medications is ascertained by a trained nurse during an interview immediately preceding the procedure. We queried the medical record for patients in whom the indication for OGD was abdominal pain (self-reported, no formal diagnostic criteria employed) and identified 20 outpatients who listed olmesartan as one of their medications. We then matched each patient by age and gender to a control patient who did not report any ARB when listing his/her medications. Using the same process, we identified

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another 20 users of non-olmesartan ARBs and corresponding matched controls. We excluded all patients with a history of coeliac disease, inflammatory bowel disease or *Helicobacter pylori* infection (present or prior). In total, we identified 80 patients undergoing OGD for abdominal pain: 20 olmesartan users with 20 matched controls and 20 non-olmesartan ARB users with 20 matched controls. This study was approved by the Columbia University Medical Center Institutional Review Board.

Abnormalities that are seen in enteropathies that include coeliac disease and the sprue-like enteropathy of olmesartan including villous atrophy, crypt hyperplasia, increased IEL concentration, chronic lamina propria inflammation and increased subepithelial collagen deposition were evaluated on routine H&E-stained slides by a gastrointestinal pathologist who was blinded to the medication status (SML). The maximum IEL count in 100 epithelial cells was counted by routine H&E stain. In addition, increased crypt apoptosis (abnormal was considered more than 2 crypt apoptotic bodies in any 10 consecutive crypts or more than one apoptotic body per biopsy piece), active inflammation (defined as any extravascular neutrophils) and eosinophilia were also documented.

Statistical analysis

We compared the prevalence of each of the above histopathological findings among ARB users and their matched controls. We used the χ^2 and Fisher exact test when comparing proportions, and used the Mann–Whitney test when comparing IEL counts. After reviewing these comparisons, we subsequently performed a post-hoc analysis comparing ARB-exposed subjects with controls with regard to the composite outcome of one or more of the following findings: architectural abnormalities (villous atrophy or crypt hyperplasia), increased IEL or chronic inflammation. In this analysis, individuals who met one or more of these aforementioned criteria were collectively compared, via χ^2 testing, to those who met none of these criteria.

All p values reported are two-sided. We used SAS V.9.3 (Cary, North Carolina, USA) for statistical calculations.

RESULTS

Among the 20 olmesartan users, the mean age was 59.5 years and 70% were women (table 1).

Among 20 non-olmesartan ARB users, the mean age was 58.5 years and 55% were women. The indication for OGD was abdominal pain in all cases and controls. When we compared duodenal biopsies of olmesartan users with controls, we identified no single histopathological finding that was significantly more frequent in either group (table 2).

However, there were variables and a composite outcome which showed trends towards significance. Of note, 10 of 20 olmesartan-exposed patients (50%) had one or more of the following sprue-like features: architectural distortion (villous atrophy and/or crypt hyperplasia), generalised increase in IEL and chronic inflammation (figure 1A–C). This compares with 4 of 20 control patients (10%, $p=0.10$). Regarding individual findings, olmesartan users had more positive findings than control patients for each variable investigated (other than increased subepithelial collagen which was not seen in any case or control), though none achieved statistical significance. Specifically, 25% of olmesartan users had foci of villous atrophy compared with 6% of control patients ($p=0.33$). The mean maximum IEL count was 13.7 in the olmesartan group compared with 10.6 for controls ($p=0.09$). Certain other features also were more common in olmesartan users than in control patients, but they too failed to reach statistical significance. The most notable of these was increased crypt apoptosis, which was seen in 25% of olmesartan users compared with 10% of controls (figure 1D).

We also compared duodenal biopsies from individuals taking ARBs other than olmesartan with patients taking no ARB. There were no statistically significant differences and no trends that suggested a similar effect (table 2).

DISCUSSION

Olmesartan is a widely prescribed ARB used in the management of hypertension. Rarely, patients taking this drug develop a life-threatening diarrheal illness with duodenal biopsies that reveal a severe enteropathy often with increased collagen deposition.[1] A study performed at our institution showed that over 10 years, 72 patients had been referred with a diagnosis of seronegative villous atrophy (negative coeliac disease serologies). The most common diagnosis in this group was seronegative coeliac disease (20 patients who had coeliac disease associated human leucocyte antigen haplotypes and responded to a gluten-free diet). The second most common diagnosis (n=19) was medication-related enteropathy. Sixteen patients had olmesartan exposure and had similar clinical and histological findings as described in the Mayo Clinic series. Eleven of the 16 olmesartan-exposed patients had increased subepithelial collagen.[2] Of considerable relevance to our study is a case reported by Talbot. The patient described was taking olmesartan, but did not have diarrhoea (presented with constipation). The patient had multiple endoscopies with biopsy. The first duodenal biopsy showed normal duodenal architecture

Table 1 Patient characteristics

	Olmesartan analysis		Other ARB analysis	
	Olmesartan users (n=20)	Matched controls (n=20)	Other ARB users (n=20) Losartan: 11 Valsartan: 3 Telmisartan: 3 Irbesartan: 2 Candesartan: 1	Matched controls (n=20)
Age (median, range)	59.5 (48–76)	59.5 (48–76)	58.5 (35–84)	58.5 (35–84)
Gender				
Male	6 (30)	6 (30)	9 (45)	9 (45)
Female	14 (70)	14 (70)	11 (55)	11 (55)

ARB, angiotensin receptor blocker.

Table 2 Histological features of olmesartan and other ARB users compared with controls

	Olmesartan analysis			Other ARB analysis		
	Olmesartan users (n=20) (%)	Matched controls (n=20) (%)	p Value	Other ARB users (n=20) (%)	Matched controls (n=20) (%)	p Value
Villous atrophy	4/16 (25)*	1/16 (6)	0.33	1/14 (7)*	2/19 (11)	1.0
Crypt hyperplasia	4/16 (25)*	2/17 (12)	0.40	3/14 (21)*	4/18 (22)	1.0
Mean maximum IEL count	13.7	10.6	0.09	13.0	18.5	0.35
Generalised IEL increase	4/20 (20)	2/20 (10)	0.67	2/20 (10)	6/20 (30)	0.24
Chronic inflammation	5/20 (25)	2/20 (10)	0.40	7/20 (35)	6/20 (30)	1.0
Eosinophilia	2/20 (10)	0/20 (0)	0.49	3/20 (15)	2/20 (10)	1.0
Neutrophilia	8/20 (40)	6/20 (30)	0.74	4/20 (20)	7/20 (35)	0.48
Increased crypt apoptosis	5/20(25)	2/20 (10)	0.40	6/20 (30)	8/20 (40)	0.74
One or more sprue-like features (architectural abnormalities, generalised increased IEL, chronic inflammation)	10/20 (50)	4/20 (20)	0.10	9/20 (45)	12/20 (60)	.34

*Villous atrophy and crypt hyperplasia was not evaluated in 4 olmesartan cases and in 6 ARB cases due to poor orientation.
ARB, angiotensin receptor blocker; IEL, intraepithelial lymphocyte.

but had increased lamina propria lymphoplasmacytic inflammation and IEL. A subsequent biopsy was similar, although showed 'mild villous blunting.' Based on the reports previously described, this patient was taken off olmesartan despite the lack of significant symptoms.[16] It is intriguing to consider whether this patient would have developed the 'full-blown' clinical and histological syndrome if he had continued to take this agent. Also of particular relevance to this study is a case, which showed similar clinical and pathological characteristics as were described in the Mayo series of olmesartan patients in a patient taking another ARB, valsartan.[17]

To determine whether olmesartan usage was associated with intestinal damage, short of the severe sprue-like enteropathy, we identified patients with abdominal pain who were taking olmesartan or other ARBs and had a duodenal biopsy. We demonstrated a trend towards sprue-like enteropathic changes in individuals taking olmesartan compared with controls. The trend towards increased crypt apoptosis is interesting mechanistically, as certain other drugs known to cause intestinal damage often demonstrate this finding (e.g. mycophenolate mofetil).[18] These changes appear to be specific for olmesartan as there were none identified in those taking other ARBs.

This is the first study to our knowledge that investigates whether exposure to olmesartan or other ARBs is associated with histopathological abnormalities among outpatients

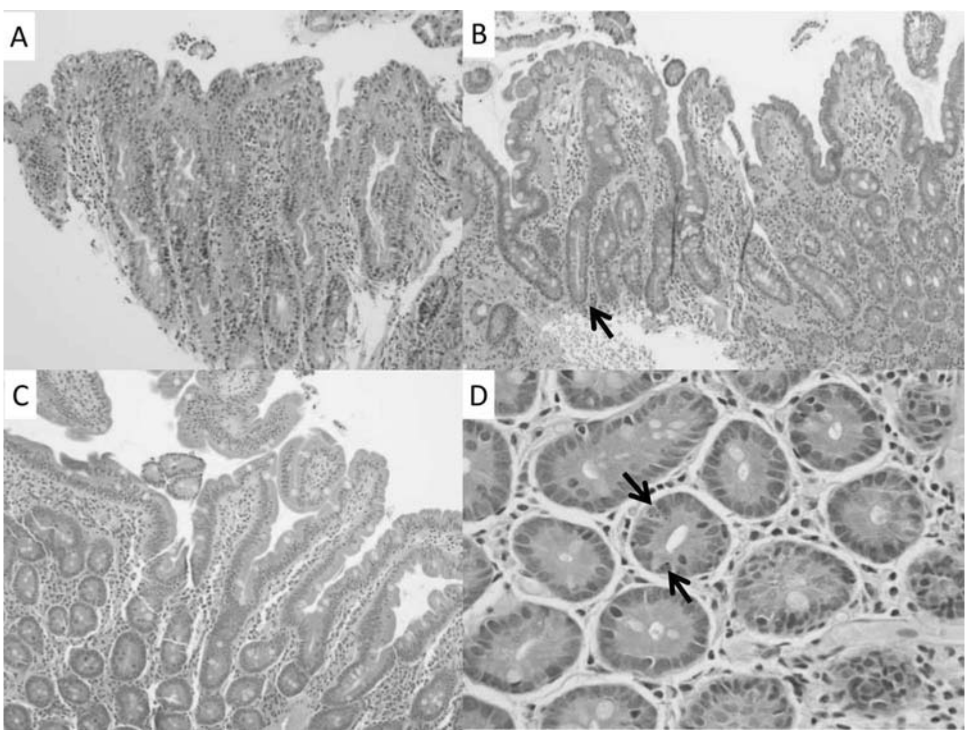

Figure 1 Highlighted findings in olmesartan users. (A) Representative photomicrograph of a small bowel biopsy from an individual showing one of several foci of villous atrophy, this particular case shows total villous atrophy but lacks intraepithelial lymphocytosis (H&E 200×). (B) A case with milder findings, including mild villous atrophy and focally pronounced crypt hyperplasia (arrow; H&E 100×). (C) This case had normal architecture, but a mild, generalised increase in intraepithelial lymphocytes (H&E 200×). (D) The case depicted in panel C also showed increased crypt apoptosis, including a crypt with 3–4 apoptotic bodies (arrows; H&E 600×).

undergoing duodenal biopsy. Our study has several limitations including its retrospective design, single centre setting and lack of information regarding duration of ARB use. We did not systematically exclude patients with known microscopic colitis; however, a post-hoc review showed that only 1 of 80 patients had microscopic colitis in our records (olmesartan user with no histopathological findings in our study). A larger sample size may have been useful, as it is possible that olmesartan causes a true increase in duodenal histopathological abnormalities but that our study was underpowered to detect this effect. Finally, we do not know whether any of the patients has subsequently discontinued olmesartan, and if so, if their abdominal pain has resolved.

This study raises the possibility that there may be a spectrum of injury associated with olmesartan use, apart from the severe syndrome that causes life-threatening diarrhoea. Further studies are needed to determine whether olmesartan use is associated with abdominal pain or other gastrointestinal symptoms and signs, as opposed to the well-characterised diarrhoea with sprue-like enteropathy. Future studies should follow-up the patients in this study to determine whether any of the olmesartan-exposed patients develop the severe enteropathic phenotype and if any of the histopathological variables we investigated are predictive thereof.

Take home messages

- This study raises the possibility that there is a spectrum of duodenal injury associated with olmesartan use.
- Angiotensin receptor blockers other than olmesartan are not associated with any histopathological findings in duodenal biopsies of patients with abdominal pain.
- Further studies are needed to determine whether olmesartan use is associated with abdominal pain and if the patients with the histopathological findings described here are at risk for developing the recently described severe sprue-like enteropathy.

Contributors SML: concept development, data collection, drafter of manuscript and guarantor of data. EDB: data collection and manuscript review. CA-G: concept development and manuscript review. GB: concept development and manuscript review. PG: concept development and manuscript review. BL: concept development, data analysis (statistics) and manuscript review.

Competing interests None.

Ethics approval Columbia University Medical Center Institutional Review Board.

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Sprue-like histology in patients with abdominal pain taking olmesartan compared with other angiotensin receptor blockers

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Exhibit 42

Comparative Effectiveness of Olmesartan and Other Angiotensin Receptor Blockers in Diabetes Mellitus

Retrospective Cohort Study

Raj Padwal, Mu Lin, Mahyar Etminan, Dean T. Eurich

Abstract—Olmesartan has been linked with increased risk of cardiovascular mortality and sprue-like enteropathy. We compared outcomes between olmesartan and other angiotensin receptor blockers in a large clinical registry of patients with diabetes mellitus. A retrospective cohort analysis using nationwide US-integrated insurance and laboratory claims was performed in 45 185 incident diabetic angiotensin receptor blocker users, including 10 370 (23%) olmesartan users. Hazard ratios were computed using time-dependant Cox models adjusted for sociodemographic characteristics, comorbidities, laboratory data, drug use, healthcare utilization, and the propensity to receive olmesartan. Blood pressure data were unavailable. Subjects were followed up for 116 721 patient-years. The primary end point was all-cause hospitalization or all-cause mortality and occurred in 10 915 (24%) patients. Average age was 54.3±9.6 years, 52% were men, 17% had cardiovascular disease, and 10% chronic kidney disease. Compared with other angiotensin receptor blockers, the adjusted hazard for olmesartan was 0.99 (95% confidence interval, 0.94–1.05) for all-cause hospitalization and mortality; 0.90 (0.62–1.30) for all-cause mortality; 0.99 (0.94–1.05) for all-cause hospital admission; 0.88 (0.78–1.00) for cardiovascular disease–related admission, and 1.09 (0.98–1.20) for gastrointestinal disease–related hospitalization in the overall cohort. Olmesartan use was associated with an adjusted hazard for the primary outcome of 1.11 (0.99–1.24) in subjects with history of cardiovascular disease and 1.21 (1.04–1.41) in subjects with chronic kidney disease. In conclusion, there is no robust signal for harm with olmesartan use. Risk may be increased in kidney disease; thus, given the widespread availability of alternate agents, olmesartan should be used with caution in this subgroup pending further study. **(*Hypertension*. 2014;63:977-983.)** • **Online Data Supplement**

Key Words: angiotensin receptor antagonists ■ cardiovascular diseases ■ comparative effectiveness research ■ hospitalization ■ mortality ■ olmesartan

Olmesartan, an angiotensin II type 1 receptor antagonist (ARB) first approved in 2002, is commonly used for the treatment of hypertension.[1] Despite being the seventh ARB approved by the Food and Drug Administration and despite a lack of hard outcome trial data supporting its use, olmesartan is widely prescribed, with estimated worldwide sales of 2 billion US dollars in 2009.[2] Two placebo-controlled randomized controlled trials examining the efficacy of olmesartan in delaying onset/progression of renal disease in patients with diabetes mellitus, Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) and Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy (ORIENT), have been recently published.[3,4] In both trials, cardiovascular mortality was increased in subjects randomized to olmesartan treatment. In ROADMAP, cardiovascular deaths occurred in 15 (0.7%) olmesartan-treated subjects and 3 (0.1%) placebo-treated subjects (P=0.01). In subjects with pre-existing cardiovascular disease taking olmesartan, 11 cardiovascular deaths occurred compared with 1 in subjects assigned to placebo. In ORIENT, 10 (3.5%) subjects receiving olmesartan died of cardiovascular causes compared with 3 (1.1%) placebo-treated subjects (P>0.05). Although these data raise concerns, they do not definitively prove harm because cardiovascular death was not a primary end point, the absolute number of cardiovascular events was low in both studies, and nonfatal cardiovascular events were not significantly different between study arms in ROADMAP (81 [3.6%] for olmesartan versus 91 [4.1%] for placebo; P=0.31).

After undertaking a safety review of olmesartan in 2011, the US Food and Drug Administration determined that the benefits of the drug outweighed its potential risks in patients with hypertension but advised against use of olmesartan for

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delaying or preventing renal disease and underscored the need for more postmarketing surveillance.[5] In 2013, following case reports describing a potential association between olmesartan and sprue-like enteropathy, the Food and Drug Administration issued a second warning and announced plans to conduct further safety reviews.[6]

The objective of this study was to provide further postmarketing assessment of the comparative effectiveness and safety of olmesartan. Specifically, we assessed the effect of olmesartan therapy compared with other ARBs on overall mortality and cause-specific hospitalization and sought to quantify absolute event rates. Given prior evidence, we hypothesized that olmesartan use would increase the risk of mortality or hospitalization relative to other ARBs in patients with diabetes mellitus, and that this risk increase would be highest in patients with pre-existing cardiovascular disease and chronic kidney disease (CKD; ie, high-risk subgroups).

Methods

We performed a population-based retrospective cohort study using an anonymized large US claims and integrated laboratory database containing information on employed, commercially insured patients with dependants from all 50 states (Clinformatics Data Mart, Optum, Life Sciences). The database has been used in multiple previous studies, contains >13 million annual lives.[7–10] We analyzed patient-level, clinically rich, deidentified longitudinal data, including administrative and demographic information (sex, age, type of insurance plan, eligibility date, and income); billable medical service inpatient, outpatient, and medical procedure claims (deidentified physician and facility identifier, date and place of service, cost of service, admission and discharge dates, procedure, and diagnosis codes); and laboratory test results and pharmacy claims data (deidentified prescribing physician, drug dispensed based on national drug codes, quantity and date dispensed, drug strength, days' supply, and cost of service). *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) clinical and procedure codes were used, and data were cleaned and analyzed using protocols compliant with the Health Insurance Portability and Accountability Act.

Research ethics review board approval to conduct this study was obtained from the University of Alberta and the New England Institutional Review Board. The procedures followed were in accordance with institutional guidelines.

Cohort Selection

An inception cohort of 114 010 new ARB users with diabetes mellitus aged ≥20 years and identified between January 1, 2004 and December 31, 2009 was created. The date of the first ARB prescription was designated as the index date. New users were individuals who did not have a prior prescription claim for any ARB for ≥1 year before their index date. We limited inclusion to subjects with ≥1 year of baseline data enrolled in a commercial medical insurance plan (Figure 1). Subjects were followed up until death, termination of medical insurance, or December 31, 2010 (study end) providing a maximum follow-up of 6 years. A priori, we decided to exclude users

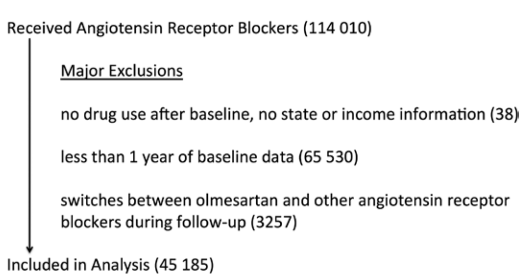

Figure 1. Inclusions and exclusions.

who crossed over from olmesartan to another ARB (or vice versa) during the follow-up period (n=3257). Mortality was ascertained by linking to the US national death index file.[11] This is a highly valid and reliable method, with >98% sensitivity when social security number data are available.[12]

The primary outcome was all-cause hospital admission or death. This composite outcome was analyzed using time-to-first event (eg, either admission date or date of death) as the dependent variable. Each component of this composite end point was also analyzed separately. Cause-specific mortality was not available. Other secondary end points included cardiovascular-related hospital admissions (*ICD-9-CM* codes 410, 411.1, 428, 430–438), the combined end point of cardiovascular-related hospital admission or all-cause mortality, gastrointestinal-related hospital admissions (*ICD-9-CM* codes 530–579), and admissions related to noninfective enteritis and colitis (*ICD-9-CM* codes 555–558). Patients were censored if they did not have an outcome of interest and reached study end (December 31, 2010) or their insurance was terminated.

Analyses

Time-varying Cox proportional hazards regression was used to estimate the effect of exposure to olmesartan (relative to all other ARBs) on each outcome. Time zero was set at index date.[13] The days' supplied field in the prescription drug dispensations database was used as a proxy for the expected duration of each prescription and was used to compute time-varying drug exposure.[14] We assumed that subjects were exposed to the drug of interest unless prescription refills were not obtained for 2 consecutive days' supplied periods. If drug discontinuation occurred, subjects were classified as unexposed from the end of the first consecutive days' supplied period to the end of the study or until they restarted the drug. In this time-varying primary analysis, outcome events were attributed to a given drug if the event occurred while the subject was exposed; no legacy or carryover effects from remote exposure were assumed.

Covariates

In addition to using time-varying exposure models to limit potential bias, additional potential confounders were included in the Cox regression models as time fixed baseline variables. These included age, sex, socioeconomic status (type of medical insurance and median household income according to the 2010 US census),[15] cardiovascular comorbidities, clinical laboratory data (glycohemoglobin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate [according to the Modified Diet in Renal Disease calculation: ≥90, 89.9–60, 59.9–30, <30 mL/min], albuminuria, and hemoglobin concentrations), and prescription drugs (eg, antidiabetic agents, antiplatelet drugs, anticoagulants, statins, calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, renin inhibitors, diuretics, and nitrates). For patients who did not have specific clinical laboratory data measured, we used the missing indicator approach for all analyses.[16]

To further control for baseline comorbidity and illness, we included an Adjusted Clinical Groups score in the model. This single comorbidity score is derived from the Johns Hopkins Adjusted Clinical Groups score system (Version 9)[17] and is weighted by 32 adjusted diagnostic groups. It performs equally to or better than the Charlson and Elixhauser comorbidity scores.[18] In addition, we adjusted for the total number of hospital admissions in the year before the index date, the total number of chronic conditions at baseline, frailty (any occurrence of malnutrition, abnormal weight loss, morbid obesity, dementia, falls, and decubitus ulcer),[17] and the time-varying propensity to receive olmesartan. For the latter, we computed the updated propensity or probability of receiving olmesartan every 3 months throughout the follow-up period.[19] This propensity score was entered into the model as a continuous probability score that was based on ≈60 variables, including demographic variables (age, sex, age–sex interaction, state, and type of insurance), socioeconomic factors (income), comorbidities, health service use, laboratory data, markers of frailty, and drug treatments. A full list of model covariates and variables included in the propensity score is available on request.

Subgroup and Sensitivity Analyses

Subgroup analyses were performed in subjects with a baseline history of cardiovascular disease and with CKD (defined as an estimated glomerular filtration rate <60 mL/min). A sensitivity analysis in which we repeated primary analysis comparing olmesartan with all other ARBs but censored subjects who switched from one ARB class to another (instead of excluding them) was also performed.

A dose–response analysis and an analysis comparing olmesartan with individual ARBs were also performed. Further methodological details are provided in the online-only Data Supplement.

Results

Of 114 010 ARB users, the final cohort comprised 45 185 subjects (Figure 1). Mean age was 54.3 (SD, 9.6) years, 52% were men, 17% had a history of cardiovascular disease, 13% had diabetes mellitus–related complications, and 10% had CKD (Table 1). We identified 10 370 (23%) olmesartan users and 34 815 (77%) who used other ARBs during the follow-up period. Additional baseline characteristics of the study population are summarized in Table 1. The prevalence of concomitant comorbidities was either equal between groups or lower in olmesartan users compared with users of other ARBs. One exception was hypertension, which was more common in olmesartan users. The average daily ARB doses prescribed during the follow-up period were olmesartan 22.1 mg, losartan 52.1 mg, valsartan 110.5 mg, telmesartan 41.9 mg, eprosartan 424.2 mg, irbesartan 145.9 mg, and candesartan 14.1 mg.

Subjects were followed up for 116 721 patient-years (median duration, 2.3 years [interquartile range, 1.1–3.8 years]). The primary composite end point occurred in 10 915 (24%) subjects; 10 836 (24%) subjects experienced ≥1 hospital admission and 458 (1%) died (Table 2).

The crude incidence rates of all-cause hospital admission or all-cause mortality were lower in olmesartan users compared with other ARBs (Table 2). However, after time-varying, multivariable adjustment was performed, the relative hazard of the primary composite end point was similar in olmesartan users (adjusted hazard ratio [aHR], 0.99; 95% confidence interval, 0.94–1.05; Table 2; Figure 2). In addition, compared with other ARB users, aHRs in olmesartan users were 0.90 (0.62–1.30) for all-cause mortality; 0.99 (0.94–1.05) for all-cause hospital admission; and 0.88 (0.78–1.01) for cardiovascular disease–related hospitalization (Table 2).

The covariate-aHR of gastrointestinal disease–related hospitalization was 1.09 (0.98–1.20) for olmesartan users compared with other ARB users and the aHR for admissions related to noninfective enteritis and colitis was 1.21 (0.87–1.69; Table 2).

Subgroup Analyses

Results in high-risk subjects are summarized in Table 3. In subjects with pre-existing cardiovascular disease, the aHR for the primary outcome was 1.11 (0.99–1.24) in olmesartan users. The aHR for the primary outcome was increased in olmesartan users with CKD (aHR, 1.21 [1.04–1.41]).

Sensitivity Analysis Censoring Rather Than Excluding ARB Switchers

In this analysis (n=48 475), the aHRs comparing olmesartan with all other ARBs for the primary outcome were 1.02 (95% confidence interval, 0.97–1.08) in the overall cohort,

Table 1. Baseline Characteristics of Olmesartan and Other ARB Users

	Olmesartan Users (n=10 370)	Other ARB Users (n=34 815)	*P* Value
Age, y	53.7±9.3	54.4±9.7	<0.0001
Sex			0.3709
Men	5472 (53)	18 197 (52)	
Women	4898 (47)	16 618 (48)	
Annual income, US dollars	48 034±6052	48 380±6237	<0.0001
Type of insurance			<0.0001
Point of service	6003 (58)	19 722 (57)	
Exclusive provider	1901 (18)	5956 (17)	
Preferred provider	889 (9)	3399 (10)	
Health maintenance	1463 (14)	5267 (15)	
Independent	108 (1)	455 (1)	
Other	6 (0)	16 (0)	
Clinical parameters at baseline			
Adjusted Diagnostic Groups Comorbidity Score	11±9	13±10	<0.0001
History of CV disease			
Ischemic heart disease	1425 (14)	6400 (18)	<0.0001
Heart failure	333 (3)	2065 (6)	<0.0001
Myocardial infarction	89 (1)	645 (2)	<0.0001
Dyslipidemia	6270 (60)	20 823 (60)	0.2339
Hypertension	9067 (87)	38 745 (83)	<0.0001
Arrhythmia	535 (5)	2463 (7)	<0.0001
Valvular heart disease	400 (4)	1698 (5)	<0.0001
eGFR categories, mL/min			<0.0001
<30	50 (0.5)	388 (1)	
30 to <60	824 (8)	3313 (10)	
60 to <90	5768 (56)	18 564 (53)	
≥90	3728 (36)	12 500 (36)	
Albuminuria (≥5 g/dL)	612 (6)	2533 (7)	<0.0001
Total cholesterol, mg/dL	192±46	190±46	0.0023
Triglycerides, mg/dL	181±174	180±195	0.7589
HDL, mg/dL	47±13	48±14	0.1175
LDL, mg/dL	112±37	109±37	0.0008
A1c, %	7.1±1.7	7.3±1.8	<0.0001
Hemoglobin, g/dL	14.1±1.6	13.9±1.6	<0.0001
Medication use			
Metformin	3404 (32)	11 988 (34)	0.0024
Sulfonylureas	1956 (19)	7525 (22)	<0.0001
Thiazolidinediones	1579 (15)	5951 (17)	<0.0001
Insulin	1032 (10)	4511 (13)	<0.0001
RAS blocker (ACE inhibitor or direct renin inhibitor)	4148 (40)	13 509 (39)	0.0282
Statins	4026 (39)	13 689 (39)	0.3641
β-Blockers	2610 (25)	9384 (27)	0.0003
Dihydropyridine CCB	1805 (17)	5494 (16)	<0.0001
Non-dihydropyridine CCB	602 (6)	2119 (6)	0.2906
Nitrates	336 (3)	1545 (4)	<0.0001

(*Continued*)

Table 1. Continued

	Olmesartan Users (n=10 370)	Other ARB Users (n=34 815)	*P* Value
Diuretics	2641 (25)	8574 (24)	0.0820
Anticoagulants	227 (2)	1073 (3)	<0.0001
Antiplatelets	459 (4)	2157 (6)	<0.0001
Healthcare utilization			
Inpatient hospitalization in year before index?			<0.0001
0	9473 (91)	30 438 (87)	
1	744 (7)	3404 (10)	
≥2	153 (1)	973 (3)	
Frailty	429 (4)	1536 (4)	0.2282
Chronic conditions in year before index date			<0.0001
≤1	1900 (18)	6373 (18)	
2–5	6653 (64)	20 540 (59)	
≥5	1817 (18)	7902 (22)	
Medication possession ratio for DM-related medications	0.44±0.7	0.47±1.0	0.0005

Data are n (%) or mean±SD. A1c indicates hemoglobin A1c; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CV, cardiovascular; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and RAS, renin angiotensin system.

1.07 (0.93–1.24) in pre-existing cardiovascular disease, and 0.91 (0.82–1.01) in CKD.

Dose–Response Sensitivity Analyses

Results of the dose–response analysis are summarized in Table S1 in the online-only Data Supplement. In the overall cohort and in the cardiovascular disease subgroup, higher doses of olmesartan were associated with significantly increased risk for the primary outcome. The dose–response analyses for valsartan showed similar results to olmesartan. However, the dose–response analysis for losartan did not show increasing risk with higher doses (Table S1).

Results of the analysis comparing individual ARB agents are summarized in Table S2. In this sensitivity analysis, olmesartan was not consistently associated with the highest risk of harm. Few statistically significant differences were found between agents. Exceptions were that losartan was associated with a borderline statistically significant increase in the primary end point in subjects with cardiovascular disease, and the other ARBs (candesartan, eprosartan, and irbesartan) were associated with a lower risk for the primary end point in the CKD subgroup only (Table S2). In both cases, this result was driven by significant reductions in hospitalizations but not mortality (data not shown).

Discussion

In this analysis of a clinically rich data set encompassing >45 000 patients with diabetes mellitus, after extensive multivariable adjustment, we found that olmesartan use compared with other ARB use was not associated with an increased risk of hospitalization or all-cause mortality in the overall cohort. In fact, there was a trend toward a lower relative hazard for cardiovascular hospitalizations. However, in the higher-risk subjects (those with pre-existing cardiovascular disease or CKD), the aHRs for this primary end point were increased, and this risk increase was statistically significant in subjects with CKD (however, this finding was not robust to sensitivity analysis). The increased risk was primarily driven by an increase in the relative hazard of all-cause hospitalization. When we examined cause-specific hospitalization, we found no statistically significantly increased risk for cardiovascular disease–related and gastrointestinal disease–related hospitalization. A dose–response analysis of olmesartan found an increased risk for the primary end point in the overall cohort and in subjects with cardiovascular disease. However, similar findings were observed in a dose–response analysis for valsartan (but not losartan). This suggests that higher doses might have been a marker of increased risk rather than a causative factor. Finally, in the agent-specific analysis, olmesartan was not consistently associated with the highest risk, and few statistically significant differences between agents were found. In aggregate, our results do not demonstrate a robust signal for harm with olmesartan use in patients with diabetes mellitus, with the possible exception of diabetes mellitus with CKD.

One prior, large retrospective cohort analysis comparing olmesartan with other ARBs has been published.[20] This study of 118 700 subjects enrolled in a single US national healthcare plan reported that olmesartan use was associated with a lower risk of cardiac events compared with valsartan,

Table 2. Outcome Comparisons in Olmesartan Users vs Users of All Other Angiotensin Receptor Blockers

Outcome	Time at Risk (Person-Years)	Events , n (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	*P* Value
All-cause hospitalization or mortality	16 040	1686 (16)	0.87 (0.83–0.92)	0.99 (0.94–1.05)	0.89
All-cause mortality	18 310	35 (0.3)	0.67 (0.47–0.97)	0.90 (0.62–1.30)	0.56
All-cause hospitalization	16 040	1678 (16)	0.87 (0.83–0.92)	0.99 (0.94–1.05)	0.91
CV disease–related hospitalization	17 951	311 (3)	0.67 (0.59–0.75)	0.88 (0.78–1.00)	0.051
GI disease–related hospitalization	17 647	498 (5)	0.98 (0.88–1.08)	1.09 (0.98–1.20)	0.10
Noninfective enteritis and colitis-related admissions	18 247	46 (0.4)	1.05 (0.75–1.47)	1.21 (0.87–1.69)	0.26

Models adjusted for age, sex, socioeconomic status, cardiovascular comorbidities, clinical laboratory data, prescription drugs, Adjusted Clinical Groups score, total number of hospital admissions in the year before the index data, total number of chronic conditions at baseline, frailty, and the time-varying propensity to receive olmesartan. CI indicates confidence interval; CV, cardiovascular; GI, gastrointestinal; and HR, hazard regression.

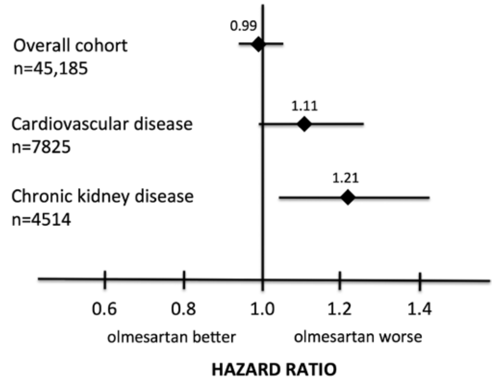

Figure 2. Adjusted hazard ratios and 95% confidence intervals for all-cause hospital admission or all-cause death according to olmesartan exposure.

irbesartan, and losartan. A limitation of this analysis was that olmesartan was prescribed to lower risk individuals, and no propensity score adjustment was used. In addition, the study population was broad and not limited to subjects with type 2 diabetes mellitus and no high-risk subgroup analyses were performed. Thus, although these findings are broadly consistent with the results of our study, they are not directly comparable because of differences in study populations and methodologic approaches.

Olmesartan is a third-generation high-affinity ARB with a 12- to 15-hour half-life that is prescribed once daily.[1,21] It is available as a dual combination product with hydrochlorothiazide or amlodipine and as a triple combination preparation with both of these agents.[21] No clinical trials demonstrating reductions in cardiovascular morbidity and mortality outcomes have been published.[22] The ongoing 1147 patient Supplemental Benefit of an Angiotensin Receptor Blocker in Hypertensive Patients with Stable Heart Failure Using Olmesartan (SUPPORT) trial is evaluating the efficacy of olmesartan compared with non-ARB antihypertensives in reducing a composite of all-cause mortality, nonfatal acute myocardial infarction, nonfatal stroke, and hospital admissions for heart failure.[23] Results are expected in 2013 to 2014.

Potential mechanisms to explain the association between olmesartan use and increased hospitalizations are not known. A J-curve mechanism resulting from excessive diastolic blood pressure lowering has been proposed to explain increased cardiovascular risk with olmesartan use in placebo-controlled studies.[3,4] Notably, previous studies comparing olmesartan with either placebo or atenolol therapy have reported that olmesartan leads to comparatively favorable improvements in such surrogate cardiovascular end points as vascular remodeling, endothelial dysfunction, inflammatory biomarkers, and atherosclerotic plaque volume.[24–26] In addition, olmesartan has been proposed to possess potential cardiovascular benefits compared with other ARBs because it is an inverse agonist at the angiotensin II type 1 receptor and because it reduces plasma angiotensin II levels.[23,27] Thus, overall, published data support the hypothesis that olmesartan should reduce rather than increase cardiovascular events. It is possible that mechanistic studies to assess potential harm have yet to be performed given that signals for potential harm have only been recently reported.

Similarly, no mechanisms to definitively explain the putative association between olmesartan and sprue-like enteropathy are known. Case reports indicate that symptoms appear months to years after olmesartan initiation.[28,29] Intestinal biopsies have revealed villous atrophy with mucosal inflammation and symptoms improve after drug discontinuation but not a gluten-free diet.[28,29] IgA transglutaminase antibodies are notably absent.[29] A cell-mediated or delayed hypersensitivity reaction, potentially associated with the human leukocyte antigen-DQ cell surface receptor type 2, has been proposed.[29]

Strengths of this study include the availability of a nationally representative, clinically rich data set; a relatively large sample size and long follow-up duration; a comparative effectiveness design in which olmesartan was compared directly against other ARBs; the use of advanced statistical techniques to adjust for potential confounders (including propensity score analysis); and conduction of extensive sensitivity analyses. Limitations include the retrospective, observational nature of the study design, the relatively short follow-up period (median 2.3 years was shorter than ROADMAP [median 3.2] and ORIENT [mean 3.2]), and the inability to adjust for additional potential confounders. The most important missing confounder was blood pressure, and we acknowledge that the observed differences in outcomes could have resulted from differences in blood pressure control. For example, in the overall cohort, subjects with losartan notably had less comorbidity at baseline, and the inability to adjust

Table 3. Subgroup Analyses in High-Risk Subjects Comparing Olmesartan Users With Users of All Other Angiotensin Receptor Blockers

	History of Cardiovascular Disease (n=8755)				CKD (GFR<60 mL/min; n=4575)			
Outcome	Adjusted HR (95% CI)	*P* Value	Time at Risk (Person -Years)	Events, n (%)	Adjusted HR (95% CI)	*P* Value	Time at Risk (Person-Years)	Events, n (%)
All-cause hospitalization or mortality	1.11 (0.99–1.24)	0.08	2008	363 (4)	1.21 (1.04–1.41)	0.02	1131	208 (5)
All-cause mortality	1.09 (0.59–2.03)	0.78	2462	12 (0)	0.88 (0.40–1.97)	0.76	1364	7 (0)
All-cause hospitalization	1.12 (0.99–1.25)	0.06	2008	362 (4)	1.23 (1.05–1.43)	0.009	1131	208 (5)
CV disease–related hospitalization	1.19 (0.98–1.46)	0.09	2335	115 (1)	1.30 (0.96–1.76)	0.09	1322	52 (1)
GI disease–related hospitalization	1.10 (0.87–1.37)	0.46	2348	91 (1)	1.27 (0.94–1.70)	0.12	1303	58 (1)
Noninfective enteritis and colitis-related admissions	1.13 (0.69–1.85)	0.62	2451	7 (0)	1.38 (0.79–2.42)	0.26	1351	9 (0)

CI indicates confidence interval; CV, cardiovascular; CKD, chronic kidney disease; GI, gastrointestinal; GFR, glomerular filtration rate; and HR, hazard regression.

for residual confounding may explain why there was a trend toward a lower hazard for the primary end point in olmesartan users in the overall group, yet risk was increased in the high-risk subgroups. Thus, it is important to emphasize that this type of study design provides associative and not causal evidence. In addition, all included subjects were middle aged Americans with commercial health insurance, which should be borne in mind when generalizing the results beyond this population. In particular, despite having cardiovascular risk factors or pre-existing disease, our study population had a crude death rate of only 392 per 100 000, which is lower than the 2010 crude death rate for all US adults aged 50 to 54 years (491.7 per 100 000)[30] and indicates that the study population was relatively healthy and well treated. Finally, we did not have information on cause-specific mortality and could not directly evaluate the association between olmesartan use and cardiovascular mortality.

Perspectives

Olmesartan is a commonly prescribed antihypertensive drug, and recent evidence linking this agent to an increased risk of cardiovascular mortality and sprue-like enteropathy mandates the need for further study. Analyses of large-scale clinical registry data serve as a useful and important complement to randomized controlled trial data in terms of assessing drug-related harm. In the present analysis, although there was a suggestion that patients with CKD may be at higher risk of all-cause mortality or hospitalization, findings that would be consistent with the results of the ROADMAP study,[3,4] our findings are not sufficiently robust or consistent to support the conclusion that olmesartan increases risk in patients with diabetes mellitus. About the subgroup of patients with CKD, given the results of ROADMAP and ORIENT and given our findings, we recommend that olmesartan use be used with caution in this patient population until further mechanistic, epidemiological, and interventional studies to clarify the effect of this drug on clinically important end points have been performed. We also recommend that further postmarketing surveillance of this agent be performed to assess risk in a more comprehensive fashion in different study samples and populations. This should take the form of additional analyses of clinical registries as well as a meta-analysis of individual patient-level data from previously published and soon-to-be-published randomized controlled trials.

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R. Padwal originated the study idea and all authors contributed to the conception and design, the analysis, and interpretation of data. D.T. Eurich and M. Lin had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. R. Padwal and D.T. Eurich wrote the initial manuscript draft, all authors revised it critically for important intellectual content, and all authors provided final approval of the version to be published. We would also like to acknowledge Betsey Jackson at Health Data Services Corporation (www.hdscorp.biz), PO Box 53, Carlisle, MA 01741 for providing independent database acquisition services.

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Novelty and Significance

What Is New?

- Olmesartan has been linked to an increased risk of cardiovascular mortality in patients with diabetes mellitus.
- We conducted a retrospective analysis of >45 000 subjects using a nationwide US-integrated insurance and laboratory claims database.
- In a risk-adjusted analysis that included propensity scores, no increased risk of all-cause mortality or hospitalization was found in our overall cohort although risk may be increased in patients with chronic kidney disease.

What Is Relevant?

- Olmesartan is commonly prescribed.
- To our knowledge, this is the first large comparative effectiveness study involving olmesartan in patients with diabetes mellitus.

Summary

We found no robust signal for harm and no compelling reason to avoid the drug except, perhaps, in patients with chronic kidney disease. Further study is required, especially in diabetics with chronic kidney disease.

Comparative Effectiveness of Olmesartan and Other Angiotensin Receptor Blockers in Diabetes: Retrospective Cohort Study

Online Supplement

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Supplementary Methods

Dose-Response Sensitivity Analysis

A dose-response sensitivity analysis was also performed in which we used a standard (i.e., non-time dependent) Cox model to examine the association between tertiles of the average daily dose prescribed (low/medium/high) and the primary outcome in olmesartan users only. Subjects with the lowest level of exposure served as the reference group. Model covariates were identical to those used in the primary analysis except the propensity score adjusted for the propensity to receive a medium or high dose of olmesartan (compared to a low dose). To account for changes in dose over time, average daily dose was calculated by dividing the total dose prescribed over the follow-up period by the total drug exposure time. To calculate follow-up time, each subject was considered exposed to the drug until an event occurred (death or hospitalization), their insurance coverage was terminated or they discontinued therapy. If insurance coverage was terminated or treatment was discontinued, subjects were censored, with a censoring date of 60 days after the date on which their last prescription had ended. We also performed the same dose-response analysis for losartan and valsartan as a further sensitivity analysis. We did this to determine whether or not findings of the olmesartan dose-response analysis were similar for another ARB or specific to olmesartan alone.

Individual ARB Analysis

As a further sensitivity analysis, we performed an individual ARB analysis by dividing the primary cohort into separate ARB groups [olmesartan, losartan, valsartan, telmisartan and all others (candesartan, eprosartan and irbesartan)] and repeated the primary endpoint analysis (models adjusted as described above) to determine if olmesartan was associated with the highest risk of all-cause hospital admission or death. Olmesartan was used as the base comparator in this analysis, which was performed in the overall cohort and in the subgroups with pre-existing cardiovascular disease and chronic kidney disease. Subjects switching ARB agents were censored at the time the switch occurred.

Table S1. Sensitivity analysis examining the dose-response relationship within users of olmesartan, losartan and valsartan.

Group	Dose Tertiles	Medium Dose vs. Low Dose aHR (95% CI)	High Dose vs. Low Dose aHR (95% CI)
Olmesartan (n=10370)			
Overall cohort	Low: <18.7 mg	1.18 (1.04-1.34)	1.20 (1.05-1.37)
	Medium: 18.7-29.8 mg		
	High: ≥29.9 mg		
Cardiovascular disease	Low: <18.6 mg	1.62 (1.21-2.17)	1.40 (1.03-1.90)
	Medium: 18.6-30.1 mg		
	High: ≥30.2 mg		
Chronic kidney disease	Low: <19.9 mg	0.77 (0.51-1.14)	1.44 (0.99-2.10)
	Medium: 19.9-32.3 mg		
	High: ≥32.4 mg		
Losartan Sensitivity Analysis (n=8656)			
Overall cohort	Low: <37.4 mg	1.06 (0.96-1.19)	0.86 (0.77-0.97)
	Medium: 37.4-60.8 mg		
	High: ≥60.8 mg		

Cardiovascular disease	Low: <35.1 mg	1.14 (0.95-1.36)	0.86 (0.71-1.04)
	Medium: 35.1-56.2 mg		
	High: ≥56.3 mg		
Chronic kidney disease	Low: <36.6 mg	1.25 (0.96-1.63)	1.10 (0.83-1.47)
	Medium: 36.7-60.7 mg		
	High: ≥60.8 mg		
Valsartan Sensitivity Analysis (n=16004)			
Overall cohort	Low: <79.7 mg	1.24 (1.12-1.37)	1.43 (1.30-1.58)
	Medium: 79.8-143.1 mg		
	High: ≥143.1 mg		
Cardiovascular disease	Low: <78.33 mg	1.58 (1.32-1.89)	1.63 (1.36-1.94)
	Medium: 78.34-139.94 mg		
	High: ≥140.0 mg		
Chronic kidney disease	Low: <80.55 mg	0.71 (0.55-0.91)	1.06 (0.84-1.33)
	Medium: 80.57-147.42 mg		
	High: ≥147.51 mg		

aHR=adjusted hazard ratio; CI=confidence interval

Table S2. Sensitivity analysis comparing all-cause hospitalization or mortality in olmesartan users versus different ARBs

Agent (compared to olmesartan)	Overall Cohort (n=45185) HR (95% CI)	Cardiovascular Disease Subgroup (n=8755) HR (95% CI)	Chronic Kidney Disease Subgroup (n=4575) HR (95% CI)
Losartan (n=8656)	1.01 (0.94-1.08)	1.22 (1.07-1.40)	1.08 (0.90-1.30)
Valsartan (n=16004)	1.02 (0.96-1.09)	1.13 (0.99-1.28)	1.02 (0.86-1.20)
Telmesartan (n=3656)	0.94 (0.85-1.03)	1.09 (0.90-1.31)	0.87 (0.66-1.14)
All other ARBs (eprosartan, irbesartan, candesartan; n=6499)	1.00 (0.93-1.08)	1.03 (0.89-1.19)	0.79 (0.64-0.98)

Hazard ratios (HR) are relative to olmesartan (n=10370).

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